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DIABETOGENIC EPITOPES

FIELD OF INVENTION

The present invention relates to proteins which are antigenic/immunogenic in pathological conditions.

BACKGROUND OF THE INVENTION

Type 1 diabetes is an autoimmune disease that results when a chronic inflammatory process of unknown origin destroys most of the insulin-producing β-cells in the pancreatic islets of Langerhans. Genetic susceptibility to diabetes is inherited and there is evidence that environmental co-factors strongly influence disease expression: <30% pairwise concordance in identical twins, 3.0% annual increase in global incidence since 1960 (Onkamo, P., et al,. (1999) Diabetologia 42, 1395-1403.), wide geographic variation and results from numerous studies in animals showing environmental factors can modify the development of spontaneous autoimmune diabetes (Scott, F. W. (1996) Diabetes/Metabolism Reviews 12, 341-359; Akerblom, H. K., and M. Knip. (1998) Diabetes/Metabolism Reviews 14, 31-67). A major unresolved issue is the identification of the environmental factors that promote the development of type 1 diabetes. This task has proven difficult because of the multifactorial nature of the disease, difficulty in linking past exposures to development of diabetes, lack of knowledge of the environmental antigens, and the large number of predisposing genes in individuals at risk (Field, L. L. (2002) Diabetologia 45, 21-35).

The two most studied environmental factors are viruses and diet. Enteroviruses may be involved but as yet, a diabetes-inducing enterovirus has not been identified.

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Epidemiological evidence of infectious hotspots or traceable routes of infection is lacking and there are conflicting data with respect to the presence of candidate viruses in the pancreas or immune cells of diabetic patients (Juhela, S. et al. (2000) Diabetes 49, 1308-1313; Foulis, A. K., et al.. (1997) Diabetologia 40, 53-61; Buesa-Gomez, J., et al. (1994) J Med Virol 42, 193-197). The highest incidence of spontaneous diabetes in Biobreeding (BB) rats and non obese diabetic (NOD) mice occurs when they are maintained in ultraclean conditions and gnotobiotic animals still develop diabetes. If animals that are maintained in strict viral-antibody-free conditions still develop diabetes, that leaves diet as the major environmental stimulus.

Although bovine proteins have been a central focus, a recent blinded, multi-center study demonstrated that a milk-free, wheat-based diet produced the highest diabetes frequency in diabetes-prone BB rats and NOD mice in three widely separate locations (Beales, P. et al., (2002) Diabetologia 45, 1240-1246), confirming numerous reports that the highest incidence of spontaneous diabetes occurs in animals fed mixed plant-based diets in which wheat is the major component. Defined diets in which wheat is the sole protein source are potent inducers of diabetes in BB rats (Scott, F. W. (1996) Diabetes/Metabolism Reviews 12, 341-359; Scott, F. W.et al. (1988) Adv Exp Med Biol 246, 277-285). In a different model of diabetes, the NOD mouse, wheat-based diets also resulted in high diabetes frequency (Coleman, D. L. et al., (1990) Diabetes 39, 432-436; Karges, W., et al., (1997) Diabetes 46, 557-564; Hoorfar, J., et al., (1993) Br J Nutr 69, 597-607; Funda, D. P., et al., (1999) Diabetes Metab Res Rev 15, 323-327). In addition, an unusually high proportion of patients with type 1 diabetes (2-10%) have wheat gluten sensitive enteropathy (celiac disease, CD) (Lampasona, V., et al., (1999) Diabetologia 42, 1195-1198), a rate that is 10-33 times that in the normal population and about 1/3 of diabetes

patients have antibodies against the CD autoantigen, tissue transglutaminase. Other reports indicate that increased peripheral blood T cell reactivity to wheat gluten was more frequent in newly diagnosed patients than in controls. These data are consistent with the involvement of dietary wheat proteins in diabetes pathogenesis.

Although considered to be a T cell mediated disease, studies of the prediction and pathogenesis of type 1 diabetes in humans rely heavily on serum autoantibodies as biomarkers of the destructive process. The humoral immune response to selected autoantigens correlates with histologic damage in the pancreas of newly diagnosed patients (Imagawa, A., et al., (2001) Diabetes 50, 1269-1273.).

The 64 kDa autoantigen originally reported in BB rat and human islets was identified in patients concordant for both the neurologic disease, Stiff-man syndrome and type 1 diabetes, as glutamic acid decarboxylase (GAD), a major autoantigen in type 1 diabetes (Baekkeskov, S., et al., (1990) Nature 347, 151-156). Despite continued progress, the antigens that initiate and maintain the process leading to β-cell destruction remain poorly understood.

The development of autoimmune type 1 diabetes involves complex interactions among several genes and environmental agents. Human patients with type 1 diabetes show an unusually high frequency of wheat gluten-sensitive enteropathy, T cell response to wheat proteins is increased in some patients and high concentrations of wheat antibodies in blood have been reported. In both major models of spontaneous type 1 diabetes, the BB rat and NOD mouse, at least half of the cases are diet-related. In studies of BB rats fed defined semipurified diets, wheat gluten was a potent diabetes-inducing protein source. A major limitation in understanding how wheat or

other dietary antigens affect type 1 diabetes has been the difficulty identifying specific diabetes-related dietary proteins.

There is a need in the art to identify proteins and nucleotide sequences encoding proteins which are diabetogenic in animals. Further, there is a need in the art to identify proteins, for example foodstuff proteins that are highly antigenic in overt diabetic animals. There is also a need in the art to develop screening processes to identify foodstuff proteins that are antigenic/immunogenic in subjects. Further, there is a need in the art to develop screening processes to identify subjects that may be at risk for developing a pathological condition due to consuming a foodstuff comprising an antigenic/immunogenic protein. There is also a need in the art to produce foods and foodstuffs in which one or more antigenic/immunogenic proteins are reduced or eliminated.